20 years of the Montreal Cystic Fibrosis Related Diabetes Screening Cohort: key insights

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Shareable abstract (@ERSpublications)
After following people with CF for 20 years, we show that CFRD is no longer associated with a worse prognosis. Mean glucose decreases slightly with CFTR modulators, but CFRD prevalence might increase with the upsurge of overweight in people with CF. https://bit.ly/4gVB5Z3

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Abstract

Introduction The Montreal Cystic Fibrosis Related Diabetes Screening Cohort (MCFC) was established in 2004 to study the prevalence, risk factors and management of cystic fibrosis-related diabetes, a significant extrapulmonary complication of cystic fibrosis with an increasing prevalence due to improved cystic fibrosis survival rates. The aims of this review are to highlight the key insights gained from monitoring the MCFC over 20 years, and to discuss the challenges and advantages of establishing such a cohort in a rare disease like cystic fibrosis.

Methods Adult people with cystic fibrosis were recruited from 2004 onward in Montreal, Canada, excluding those already diagnosed with cystic fibrosis-related diabetes. Clinical and biological results (including oral glucose tolerance tests) were recorded regularly.

Results Findings from the MCFC contributed to a better understanding of cystic fibrosis-related diabetes pathophysiology (in particular, the joint roles of reduced insulin secretion and added insulin resistance) and its relationship with lung function. Over the years, we observed a shift towards overweight and obesity among cystic fibrosis patients, along with improved lung function. This could be due to improved cystic fibrosis care and to the introduction of cystic fibrosis transmembrane conductance regulator modulators. We were also able to validate new, simplified screening modalities and management strategies (*e.g.* physical activity) for cystic fibrosis-related diabetes.

Conclusion The MCFC has contributed to the understanding of cystic fibrosis-related diabetes and informed best practice guidelines. Future research will focus on how cystic fibrosis transmembrane conductance regulator modulators influence glycaemic control and cardiometabolic health in people with cystic fibrosis.

The Montreal Cystic Fibrosis Related Diabetes Screening Cohort

"Since epidemiological data indicates that we are going to face a significant increase of cystic fibrosis-related diabetes (CFRD) in the near future, we need to be prepared" [1]. This is how Costa *et al.* [1] concluded their review on CFRD back in in 2005, at the time the Montreal CFRD screening cohort (MCFC), a prospective cohort with the aim of studying the prevalence and risk factors for CFRD in adult persons living with cystic fibrosis (CF), was established.

By 2004, the world of CF was already changing: survival rates were increasing due to improved medical management and nutritional status, and CFRD, defined as a fasting blood glucose level >7 mmol·L^{-1} or a blood glucose level >11.1 mmol·L^{-1} measured 2 h after an oral glucose challenge in people with CF, was becoming the primary extrapulmonary complication of CF. The median age at onset of CFRD was

20 years [2], with prevalence increasing with age [3]. CFRD onset often marked a turning point for people with CF, because it was associated with worse pulmonary function and nutritional status, and increased mortality rate [4, 5]. The pathophysiology of CFRD was poorly understood, particularly the respective roles of insulin deficiency and insulin resistance in the onset of hyperglycaemia. A key aim was to identify the best screening methods for CFRD, because early treatment appeared to be associated with better outcomes [6]. Unlike in more common types of diabetes, such as type 1 and type 2 diabetes, the clinical symptoms of CFRD were less typical. The oral glucose tolerance test (OGTT) was, and continues to be, considered the gold standard for screening CFRD. This is because fasting glucose and glycated haemoglobin (HbA1c, a biological marker reflecting the average blood glucose over the past 3 months in other types of diabetes) were not sensitive enough, which has been known since the early 2000s [7], [8]*. A second key objective was to determine the best management approach following CFRD diagnosis: what dietary advice should be given in the context of likely undernutrition? When and how should insulin, the only recommended medication for CFRD, be given to combine glucose control with its anabolic effects?

To gather information on the incidence, prevalence, pathophysiology, consequences and optimal treatment of an emerging complication of CF, clinical researchers from the Montreal Clinical Research Institute (IRCM) launched one of the rare, prospective, observational, long-term cohort studies for CFRD screening in North America.

The principal aims of this review are to highlight the main insights gained from monitoring this cohort over 20 years of clinical research and more than 50 published articles, and to discuss the challenges and advantages of establishing such a cohort in a rare disease like CF.

Methods

Starting in 2004, people with a confirmed diagnosis of CF who were ⩾18 years old and were followed at the Centre Hospitalier Universitaire de Montreal's CF clinic were screened for inclusion.

Exclusion criteria were as follows [9]*: received or being on the waiting list for lung transplant, active cancer of any type, transferred to another clinic (*e.g.* if the participant moved away from Montreal), known CFRD at time of recruitment, or diagnosed with CFRD at any point during the prospective study and no longer followed.

If eligible, people with CF were invited to participate in the study during their annual OGTT at the CF clinic. They needed to be clinically stable at the time of OGTT and over the month prior (*i.e.* no symptom of pulmonary infection, no use of intravenous antibiotics, no use of glucose-altering medications like oral corticosteroids, and not currently pregnant). If they were clinically unstable but otherwise met the inclusion criteria, inclusion was postponed.

For the OGTT, participants were required to fast for at least 8 h before the test, and subsequently ingest a glucose solution (glucodex, containing 1.75 g·kg^{-1}, up to 75 g of glucose). Plasma glucose levels were measured at baseline (T0) and 1 h (T60) and 2 h (T120) after ingesting the solution. This enabled the categorisation of participants into four distinct glucose tolerance categories (table 1). Once included, biological and clinical data were collected concurrently at each subsequent OGTT visit (approximately every 18 months) [9]*. If a participant met the OGTT criteria for CFRD, another test was performed within 3 months. CFRD was confirmed if the OGTT results once again met CFRD criteria, and the participant was excluded. If the results of the second OGTT did not confirm CFRD, the patient was not excluded from follow-up and was not considered to be living with CFRD.

TABLE 1 Glucose tolerance categories

Categories of glucose tolerance	Fasting glucose (mmol·L^{-1})	1-h OGTT glucose (mmol·L^{-1})	2-h OGTT glucose (mmol·L^{-1})
Normal	<7.0	<11.1	<7.8
Impaired	<7.0		7.8–11.0
Indeterminate	<7.0	⩾11.1	<7.8
Cystic fibrosis-related diabetes	⩾7.0	or	⩾11.1

OGTT: oral glucose tolerance test.

The results of the corresponding OGTT were recorded along with specific clinical and biological data (supplementary table S1). As of June 2024, 312 people with CF who were not diagnosed with CFRD at the time of inclusion or within the following 6 months were enrolled, with a median follow-up duration of 8.8 years (interquartile range 3.7–16.2 years). Approximately 90% of people with CF had at least one F508del mutation.

What have we learnt? Formal knowledge

Pathophysiology of cystic fibrosis-related diabetes

Insulin insufficiency or insulin resistance, which is the main culprit?

In all types of diabetes mellitus, hyperglycaemia stems from a lack of insulin, the hormone responsible for lowering blood sugar levels. Insulin insufficiency can be complete and result from the destruction of the insulin-secreting β-cells located in the pancreatic islets, as seen in type 1 diabetes, or from β-cell dysfunction, as seen in type 2 diabetes [10]. The latter usually results in relative insulin insufficiency, in which case hyperglycaemia will eventually develop if insulin insufficiency is associated with insulin resistance, *i.e.* an impaired response of the target cells to the effects of insulin.

However, the relative roles of insulin insufficiency and insulin resistance in CFRD genesis are still debated [11]. People with CF can present with significant insulin insufficiency but at varying degrees resulting from interrelated factors: destruction of the pancreatic islets following lesions to the exocrine pancreas and its microvascularisation, with the exocrine and endocrine pancreas being in constant exchange [12, 13]; a possible direct role of cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation on β-cell dysfunction [14]; oxidative damage and endoplasmic reticulum stress [15]; possible immune activation in the pancreas [16]; and inflammation in the pancreatic islets inducing β-cell dysfunction [17]. Indeed, a prospective study from the MCFC showed that a lower insulin-to-glucose ratio, a marker of insulin insufficiency, was associated with a higher risk of developing CFRD [18]* and was more common in subjects with CFRD, confirming older works [19, 20]. For unknown reasons, this finding appeared to be primarily observed in male people with CF [21]*. We and others [22, 23] also showed that, compared to subjects without CF, all people with CF had a defect in early insulin secretion in response to OGTT even if they had normal glucose tolerance (NGT). The disposition index, which reflects the ability of β-cells to compensate for insulin resistance, was decreased in people with CF, even more so if they were glucose intolerant [9]*. This concurs with works from other CF teams [24], who also showed that people with CF with impaired glucose tolerance (IGT) or CFRD presented with signs of β-cell damage, as evidenced by elevated proinsulin levels [25]. This could imply that avoiding hyperglycaemia might alleviate excessive insulin demand and protect β-cells in people with CF with early signs of glucose intolerance.

However, we were also able to show that insulin resistance was similar between control subjects and people with CF with NGT, but was significantly higher in people with CF with IGT or CFRD [9]*. In other words, glucose intolerance in people with CF was associated with insulin resistance, which was confirmed in another subset of people with CF: adult men with CF and higher alanine aminotransferase levels (a biomarker of liver damage) had higher insulin resistance and were at higher risk of CFRD [26]*. This has also been shown by other teams [27, 28]. We also performed a prospective study on a subset of people with CF from the MCFC without known CFRD who underwent two OGTTs 22 months apart. Insulin secretion was reduced but remained stable over the study period; however, insulin resistance increased in people with deteriorated glucose tolerance, decreased in people with improved glucose tolerance, and remained stable in people without changes [29]*. Similarly, we revealed that in people with CF who were >35 years old and had a mean prospective follow-up of 10 years, insulin secretion remained low and stable. However, insulin resistance increased in people who developed abnormal glucose tolerance whereas it remained stable in people with NGT [30]*. Interestingly, other CF teams failed to confirm the role of insulin resistance in the onset of CFRD [31–33]. This could be due to the use of less sensitive tests to assess for insulin resistance in people with CF: while the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is widely used in people living with type 2 diabetes, we showed that it does not reflect insulin resistance well in people with CF [34]*, confirming the work of Toin *et al.* [35]. The index proposed in 2001 by Stumvoll *et al.* [36] was a better marker than other indexes. In favour of this hypothesis, Nielsen *et al.* [37] also used the Stumvoll index and found that insulin resistance increased with incremental impairment in glucose tolerance. Additionally, teams who performed a direct evaluation of insulin resistance using a hyperinsulinaemic–euglycaemic clamp confirmed that people with CF with IGT were more resistant to insulin than people with CF with NGT [38, 39].

In summary, we have shown that people with CF develop early impairments in insulin secretion. Insulin resistance (*e.g.* secondary to chronic inflammation, as seen with the improved glucose tolerance observed after lung transplantation in people with CF with CFRD [40]) may accelerate CFRD onset. In fact, we

recently demonstrated that the hazard ratio of developing CFRD was higher in people with CF with both low insulin secretion and high insulin resistance than in those with isolated low insulin secretion or high insulin resistance [34]*.

Systemic factors with a potential impact on insulin secretion and resistance

Weight and adiposity

Maintaining a sufficient weight has long been one of the goals and challenges of people with CF, but better nutritional and pulmonary management (possibly even with excessively high energy intake goals [41]) followed by the more recent use of CFTR modulators have enabled the gradual emergence of a group of people with CF with overweight or obesity: the prevalence of overweight/obesity in people with CF increased from 5–10% [42] in the 2000s to 30–35% in the 2020s [43]. Confirming other studies [44, 45], Bonhoure *et al.* [46]* showed that overweight and obesity were associated with older age, less pancreatic insufficiency and certain unfavourable cardiometabolic factors such as higher systolic blood pressure and higher insulin resistance. Similarly, people with CF who had prospectively gained weight over the observational period (mean duration of follow-up: 3.5 years) had higher triglyceride levels and higher insulin resistance. However, glucose tolerance did not differ according to weight status or weight variations. Being overweight was not associated with CFRD, but was associated with better pulmonary outcomes [46, 47]*, as was shown by other teams [48, 49]. Similarly, people with CF with low levels of high-density lipoprotein cholesterol or with hypertriglyceridaemia were not prospectively at higher risk of developing CFRD, albeit having a higher fat mass [50]*. This could partly be explained by the fact that leptin levels were higher in people with CF with high adiposity, which was associated with increased insulin secretion [51]*.

CFTR modulator therapies are designed to correct the defective protein encoded by the *CFTR* gene. They are transformative treatments that have a proven effect on the number of pulmonary exacerbations, pulmonary function and weight gain. The most effective treatment to date, elexacaftor/tezacaftor/ivacaftor (ETI) (brand name Trikafta), has been publicly approved and funded in Canada since 2021. ETI initiation is proven to be associated with important weight gains, predominantly secondary to an increase in fat mass [52]. In fact, an overall improvement in nutritional status after ETI initiation was noted in a recent study, as demonstrated by an increase in Nutritional Risk Index, a tool that measures malnutrition and predicts clinical outcome [53]. Interestingly, Gramegna *et al.* [54] showed that people with CF with underweight gained more weight with ETI than other people with CF (+4.6 kg, +3.2 kg and +0.7 kg at 6 months for people with CF with underweight, normal weight and overweight, respectively), but going from normal weight to overweight was not uncommon.

One of our future aims is to assess the impact of CFTR modulators on weight trajectories and to assess the putative complications of weight gain in people with CF.

Nutrition

Unsurprisingly, people with CF from the MCFC often exhibited multiple nutrient deficiencies, likely stemming from malabsorption and exocrine pancreatic insufficiency. Our research indicated that 22% of people with CF had zinc deficiency (concurring with other studies [55, 56]), 66% had suboptimal levels of vitamin K (in line with existing literature [57]) and 58% had suboptimal levels of vitamin D (again, similar to what has been described elsewhere [58]). As previously known, zinc deficiency correlated with lower forced expiratory volume in 1 s (FEV_1) and impaired bone health, but we also discovered a correlation between zinc deficiency and risk of CFRD (63% of zinc-deficient people with CF had CFRD, compared to 43% of those with sufficient zinc), possibly due to zinc's involvement in insulin synthesis, secretion and action [59]*. Suboptimal vitamin K levels were associated with an increased risk of *Pseudomonas aeruginosa* colonisation and lower body mass index (BMI), but we also newly showed that vitamin K was associated with lower insulin secretion [60]*. Contrary to other study findings [61, 62], we did not find any correlation between vitamin D deficiency and glucose tolerance assessed with OGTT or HbA1c [63]*.

The complex relationships between cystic fibrosis-related diabetes and the lungs

Traditionally, the onset of CFRD has been linked to an increased risk of deteriorating nutritional status and pulmonary function, evidenced by declines in BMI and FEV_1 occurring 2–4 years before CFRD diagnosis [4, 64, 65]. In a prospective study, lower insulin secretion was also associated with higher rates of pulmonary function declines [66]. Accordingly, we showed that increased area under the curve (AUC) of glucose at OGTT, high plasma glucose at 60 min of the OGTT, and decreased insulin secretion were all correlated with reduced pulmonary function [9, 67, 68]*, while Gileles-Hillel *et al.* [69] showed that the AUC of glucose was associated with an increased number of pulmonary exacerbations. Furthermore, we found that people with CF had subclinical chronic inflammation, with elevated levels of fibrinogen.

Inflammation was more severe in case of glucose intolerance, given that C-reactive protein levels, a marker of systemic inflammation, were elevated only in people with CF with CFRD [70]*. This is in accordance with the study by Montemari *et al.* [71], which showed that C-reactive protein correlated with HbA1c levels in people with CF. YKL40, a protein that plays a role in inflammation and tissue remodelling and is associated with the severity of diverse pulmonary diseases, was also elevated in people with CF, especially if they had dysglycaemia [72, 73]*. This chronic inflammation, combined with possible cytokine secretion (*e.g.* interleukin-17 [74]*), common pulmonary exacerbations, corticosteroids treatments and, more recently, possible obesity, could explain the progressive onset of insulin resistance [75].

When it comes to specific pathogens, we showed in a prospective study that the prevalence of *Stenotrophomonas maltophilia* colonisation was higher in people with CF with glucose intolerance than in those with NGT, but was not associated with glucose tolerance evolution [76]*. This was also the case with *Burkholderia cepacia* [77]. People with CF with *Stenotrophomas* colonisation and dysglycaemia had more pulmonary exacerbations than people with CF with NGT [76]*.

However, our recent studies revisiting the relationship between CFRD and the lungs no longer found evidence supporting a correlation between high blood glucose and decreased FEV_1 or its decrease over a prospective 4-year period [78]*. Even though our prospective studies were conducted before the introduction of CFTR modulators, the onset of CFRD was no longer preceded by declines in pulmonary function or BMI [79]*. Living with CFRD was not associated with poor FEV_1 recovery following pulmonary exacerbations in other cohorts either [80]. Similarly, in a comparative study between people with CF from the MCFC and a French cohort, we observed that Canadian people with CF had a higher BMI and a higher incidence of new-onset CFRD over a 4-year prospective period than their French counterparts (19.2% *versus* 9.8%, respectively), but exhibited better lung function [81]*.

The absence of a correlation between CFRD and impaired lung function can be attributed to advancement in CF management and nutritional care over the last decade [82], but could also be attributed to a more refined understanding of CF pathophysiology and improved management of analytical biases. Indeed, Potter *et al.* [79]* found that the association between glycaemia and FEV_1 was mainly mediated by BMI, concurring with Granados *et al.* [83], who showed that young people with CF with CFRD had a lower fat mass index and lower weight than people with CF with NGT, but a similar FEV_1. More recently, we found that genotype and exocrine pancreatic insufficiency were common denominators between higher blood glucose and lower FEV_1 [79, 84]*. Exocrine pancreatic damage, in addition to being a marker of CF severity, may also be one of the causal factors in the onset of CFRD [85].

Thus, we hypothesise that glucose intolerance is a marker of CF severity, which explains the differences in FEV_1 results between glucose tolerance groups, even in early childhood [86], and especially in earlier studies. But with improvements in nutritional care, respiratory care and glucose management, and with the advent of CFTR modulators, the once-established link between CFRD and overall worse prognosis (*i.e.* higher risk of lower pulmonary function and losing weight) is gradually being called into question. This, along with the evolution of pancreatic exocrine function, will be one of the clinical aspects to monitor in the upcoming years, especially in people with CF treated with CFTR modulators.

What have we learnt? Clinical knowledge

Screening for cystic fibrosis-related diabetes

Studies performed within the MCFC have expanded our understanding of CFRD and allowed us to explore more practical questions, with the primary focus being the modalities of CFRD screening. Early detection and treatment of CFRD improve the overall prognosis for people with CF [87], especially children [64]. Moreover, among young people with CF with CFRD, those who were followed in centres that screened more regularly for CFRD had slower rates of decline in pulmonary function, highlighting the beneficial effect of early CFRD treatment [88].

However, the OGTT, the reference test for CFRD screening, is time-consuming for both people with CF and healthcare professionals, can cause nausea and fatigue, and can yield results that are frequently not reproducible, as we and others have shown by repeating OGTTs prospectively [29]*, [77, 89]. Rates of screening are therefore suboptimal: only 29–48% of people with CF actually take their annual OGTT [90].

Hence, our first step was to reassess OGTT's performance in screening for CFRD. We demonstrated that established indices of insulin secretion based on OGTT values were reliable for evaluating insulin secretion in people with CF [91]*. We also found that various timepoints of the OGTT were informative for CFRD screening and CFRD risk prediction. The maximum OGTT glucose level was associated with the

prospective risk of developing CFRD and a level <8 mmol·L^{-1} could identify people with CF at very low risk of developing CFRD [92]*. Additionally, people with CF who had combined indeterminate glycaemia and IGT (table 1) were at a higher prospective risk of developing CFRD compared to those with NGT [93]*. Interestingly, 22% of people with CF, primarily men and those with NGT, experienced hypoglycaemia during the OGTT. This was associated with a considerably lower prospective risk of developing CFRD, especially in the case of level 2 hypoglycaemia (*i.e.* plasma glucose <3 mmol·L^{-1}) [94]*, in contrast to what had been described by Radike *et al.* [95], who showed a stable risk of CFRD whether the people with CF experienced hypoglycaemia at OGTT or not.

Owing to the challenges of maintaining annual OGTT adherence, the next step was to explore methods to simplify the OGTT process for people with CF. We showed that people with CF but without CFRD were often unaware of the mechanisms and consequences of CFRD [96]*. Additionally, they were apprehensive about discovering they might have CFRD, fearing it would lead to a request for significant lifestyle changes and altered quality of life, as shown by Kwong *et al.* [97]. We thus advocate for providing clear information about CFRD and about the potential positive consequences of early treatment of CFRD because this is highly important for people with CF [96]*. On a more technical note, we showed that a 90-min OGTT could serve as a reliable alternative to the standard 120-min test, allowing a shorter test [98]*. Other studies showed that elevated glucose at 60 min is a better indicator of respiratory symptoms than other OGTT timepoints [99], but this is still debated [100]. We also demonstrated that performing the OGTT at home is feasible and preferred by people with CF, although it is not completely reliable [101]*.

The third step involved evaluating alternative screening modalities for CFRD. We showed that isolated fasting hyperglycaemia is not appropriate for CFRD screening, because it was present in only 8% of participants and did not indicate a higher risk of CFRD. However, people with CF with both fasting hyperglycaemia and IGT were at higher prospective risk for CFRD than those with IGT alone [102]*, as shown by Schmid *et al.* [103]. Regarding HbA1c, our initial study confirmed the findings of other studies [7, 104] and found no correlation between mean plasma glucose and HbA1c in people with CF [105]*, but subsequent studies showed that an HbA1c level >6% is associated with a high prospective risk of developing CFRD [106]*. We found that a threshold of 5.8% [107] was not sensitive enough to screen for CFRD [8]*. However, using prospective data, we further validated a proposal by Gilmour *et al.* [108] of using the new, lower HbA1c threshold of 5.5% as the first step of a two-step screening method [109]* to select people with CF who must undergo an OGTT. This approach proved to be feasible and reliable [8, 90]*, potentially reducing the need for annual OGTTs by 22.7% to 50.7%. Consequently, this method is now recommended in Canadian clinical practice guidelines [110]*. Another promising method involves the use of continuous glucose monitoring (CGM) devices, which are now widely available. CGMs record 10–14 days of interstitial glucose data, providing detailed insights into glycaemic variations throughout the day, including pre- and post-meal periods, physical activity and sleep. They are easy to install and are minimally invasive. CGM results seem to be more closely associated with the general clinical state of people with CF than OGTT results [111–114], and to be more reproducible [115]. However, CGM and OGTT do not measure the same aspects of glucose regulation and thus their results do not always correlate [116]. In addition, diagnostic thresholds for CFRD and other types of diabetes screening using CGMs are still being defined. Different CF teams worldwide, including ours, are currently evaluating which CGM parameters should be used in this context [117]*.

Intervention studies

After discussing CFRD screening modalities, the next logical question was how to manage glucose intolerance or CFRD if detected. Until recently, the recommendations were straightforward: for people with CF, regardless of glucose tolerance status, a diet rich in fats and carbohydrates was advised to avoid undernutrition due to exocrine pancreas insufficiency. Insulin was the only proposed medication because of its powerful combined glucose lowering and anabolic effects. However, as mentioned earlier, overweight and obesity are becoming increasingly common among people with CF, especially with the introduction of CFTR modulators, which have led to considerable weight gain in some people with CF. This increases the risk of cardiometabolic abnormalities, such as hypertension or dyslipidaemia, which until recently were rare in people with CF, thereby potentially raising cardiovascular risk, especially in conjunction with CFRD [46]*. This prompted us to conduct studies on diet and physical activity in people with CF. We found that people with CF with CFRD had more glucose fluctuations compared to those with NGT or IGT. However, the proportion of fat, carbohydrates and proteins in a 3-day food diary, as well as the number of steps walked per day, did not affect these glucose fluctuations [118]*. This contrasts with the study by Armaghanian *et al.* [119], who showed that people with CF who had higher glycaemic index intakes were in the hyperglycaemic range for a longer time. However, a 12-week combined exercise programme was associated with reduced total glucose excursions, lower 120-min blood glucose levels at OGTT and lower

insulin resistance in people with CF with abnormal glucose tolerance [120]*. In another recent study, we showed that repeated short bouts of physical activity could help lower early post-prandial glycaemia peaks in people with CF [121]*. These findings were similar to a study showing that virtual personal training was feasible in adolescents with CF and helped increase insulin secretion [122], but discordant with another study that found no difference in blood glucose levels in people living with CFRD, whether they performed 150 min of moderate physical activity per week or not [123].

Other intervention studies, such as those testing vitamin D (by implementing an intensive supplementation protocol which normalised vitamin D levels in people with CF) or fibre supplementation, revealed no effect on blood glucose levels [124–126]*.

Thus, the MCFC provided us with new insights regarding the pathophysiology of CFRD and its clinical impact, particularly its links with lung function. It also enabled us to explore the various possibilities for simplifying CFRD screening, and to test different interventions for optimal management of overt CFRD.

20 years of follow-up, a long and winding road

Snakes…

Establishing and sustaining a long-term prospective cohort to monitor people with a rare disease is a challenging endeavour. First, one of the hardest tasks is finding durable funding. Moreover, due to the extended follow-up duration, the researchers overseeing the cohort are likely to change over time, necessitating ongoing effort to uphold the study's consistency and continuity. Finally, the COVID-19 pandemic created another major and unexpected barrier. Performing OGTTs was no longer a priority for the hospital, and resuming CFRD screening was far down the list of tasks to be accomplished. Fortunately, due to vaccine development and improved epidemiological conditions, we resumed follow-up appointments and recruitment in January 2024, implementing several changes (use of the two-step screening method according to the new Canadian guidelines [110]*, retrospective collection of missing data, addition of follow-up data for people with CF diagnosed with CFRD, and creation of an online database to manage and secure data).

…and ladders

While we did encounter a number of difficulties, the MCFC also has many advantages.

First, even in the era of big-scale registries (*e.g.* the Canadian CF Registry [127], the European Cystic Fibrosis Society patient registry [128] and the Cystic Fibrosis Foundation patient registry [129]), using data from a locally managed cohort can be both easier (with ease of access to up-to-date data) and cheaper for research teams. The MCFC captures more detailed, granular and standardised data, including patient-level information such as glucose and insulin measurements from repeated OGTTs over multiple years, as well as experimental biomarkers like inflammation markers derived from plasma and serum samples: these data are difficult to collect consistently in national registries. More importantly, the MCFC enables mechanistic studies and the investigation of novel interventions with subsets of voluntary participants, often serving as a testing ground for hypotheses that can later be validated in larger, population-based registries. In addition, it allows researchers to design exploratory or interventional studies with subsets of voluntary participants from the cohort [120]*, and to describe the immediate and long-term effects on the cohort population of new measures implemented in the clinic (such as increasing vitamin D intake [125]*).

Second, working with a cohort rather than big-scale registries allows prospective studies to be performed more easily. Approximately one third of the studies carried out using the MCFC data used prospective analyses. Prospective studies make it possible to check the validity of tests that are repeated over the years (*e.g.* OGTTs [29]*), to study the risks associated with certain factors or exposures (*e.g.* the risk of developing diabetes over the years in people with CF with decreased insulin secretion at baseline [18]*) or to determine whether changes in different variables share a correlation (*e.g.* evolution of glucose tolerance at OGTT and evolution of insulin resistance [29]*). These long-term studies also provide more reliable information about complications that occur after many years of disease progression. Thus, in the next few years, the MCFC should enable us to learn more about the long-term complications of metabolic syndrome and of CFRD in the era of CFTR modulators.

Third, from an organisational standpoint, more than 30 students, including medical and undergraduate interns, as well as graduate students, have analysed data from the MCFC, resulting in over 50 publications. Principal findings have been shared through over 80 posters and oral presentations at national and international conferences. Importantly, collaborations have been established with researchers in Canada,

France and the USA. Additionally, we have engaged patient partners to identify research priorities for people with CF, published lay language articles and organised webinars to facilitate knowledge transfer.

MCFC specificities foster tangible benefits for both healthcare professionals and people with cystic fibrosis

People with CF have been prospectively followed in the MCFC for 20 years now.

Other prospective cohorts have been following people with CF throughout the world and have helped widen our understanding of CF natural history. However, the MCFC presents with specific features: the majority of cohorts following people with CF mainly explore the pulmonary aspects of the disease and provide answers on the overall survival or respiratory status of their participants [130, 131], whereas the MCFC focuses on metabolic features of people with CF.

Several cohorts have been following children living with CF since infancy and exploring their glucose tolerance, but data after their transition to adulthood are not available yet [132, 133], while the MCFC follows adult people with CF, including those >50 years old.

Other teams have studied the nutrition of people with CF [41], but with a greater focus on undernutrition, and less on CFRD or metabolic syndrome, while the MCFC gathers information on BMI, blood pressure, lipid levels, glucose tolerance, insulin rates and medication usage for CFRD, hypertension and dyslipidaemia.

Researchers from France (from the Strasbourg and Lyon teams) have similar objectives to ours [40, 134]; they also study glycaemic control and the use of new technologies in people with CF. However, they are more focused on treatments and transplantation, and less on metabolic syndrome in a broad sense. Our approaches are, however, complementary and we are currently working on collaborative projects.

Thus, the MCFC is one of the few cohorts able to report long-term, prospective data about the clinical and metabolic status of adult people with CF, some of whom are now >60 years old. This will enable us to describe the effects of ageing in people with CF, one of the major concerns of the years to come. Moreover, data from our cohort have broadened scientific knowledge about CFRD screening, nutrition and metabolic syndrome (*e.g.* we were among the first to describe the characteristics of people with CF with dyslipidaemia, overweight or obesity). Compared with the Germany/Austria cohort [135], which retrieves information on CFRD from a registry for people living with diabetes from all causes [136], the MCFC is lacking data on the long-term consequences of established CFRD, but we have now added an amendment allowing participants who had been excluded due to CFRD diagnosis to re-enter the cohort by consenting to a new form.

The MCFC will thus be able to provide access to CFRD-specific data that cannot be obtained from diabetes or CF registries alone, because our database has been specifically designed to gather information on all aspects of CFRD and metabolic complications in people with CF: pulmonary data (FEV_1, number of bouts of antibiotics per year, bacterial colonisation), diabetes data and medication data (treatments for respiratory symptoms, diabetes management and complications, metabolic comorbidities and mental health complications are recorded).

The formal and clinical knowledge acquired from analysing data from the MCFC, combined with our collaborations and comprehensive literature review, led us to develop the first Canadian best practice guidelines for CFRD [110]*. In these guidelines, we recognise the evolving paradigms of CFRD in recent years and derive practical recommendations aimed at simplifying screening and management of CFRD. These measures have the potential to improve the quality of life of people with CF in the years ahead.

We are witnesses to a changing disease

In summary, the data obtained thanks to the ongoing participation of the people with CF of the MCFC have enabled us to conclude that:

- CFRD occurs in a context of impaired insulin secretion, but added insulin resistance is an additional factor that eventually leads to overt CFRD. Insulin resistance should be assessed using dynamic indexes following a glucose charge rather than fasting based indices, because HOMA-IR is not sensitive enough in people with CF.
- Overweight and obesity are becoming increasingly common in people with CF and may result in specific clinical characteristics that should be monitored in the upcoming years: overweight and obesity are not

correlated with higher rates of CFRD but the insulin resistance associated with obesity in people with CF could, in the long term, lead to a type of diabetes that more closely resembles type 2 diabetes.
- The once-established quicker deterioration of lung function and overall worse prognosis preceding the diagnosis of CFRD are gradually being called into question.
- New, simpler CFRD screening and management (*e.g.* physical activity) modalities can be considered in this context.

However, all this knowledge will likely need to be re-evaluated in the age of CFTR modulators: their use, especially the use of ETI, has transfigured the prognosis and consequences of CF. It is now generally accepted that people with CF who take these medications will find that exacerbations are significantly reduced, lung function is in constant improvement and weight can increase rapidly. However, the metabolic impacts of CFTR modulators remain to be fully elucidated. With life expectancy anticipated to increase over the next decade, age-related diseases that have been uncommon among people with CF may begin to emerge. Moreover, knowledge regarding the effects of CFTR modulators on CFRD remain equivocal. Some studies show a beneficial effect of CFTR modulators on glycaemia in people with CF with glucose intolerance [137–139], likely owing to their ability to reduce insulin resistance by preventing chronic inflammation and recurrent exacerbations, and possibly preserving β-cell function [140]. The effects of CFTR modulators on glycaemia are however less obvious in people with CF with NGT [141]. Conversely, significant weight gain is becoming more common in people with CF. Up to now, we had shown that being overweight or having hypertriglyceridaemia, despite being associated with higher insulin resistance, were rather signs of milder disease and of lower pulmonary risks [142]*. However, overweight is often accompanied with increased blood pressure and dyslipidaemia [46]*. Weight gain, along with possible hepatic effects resulting from CFTR modulator treatment, could lead to increased insulin resistance and higher prevalence of CFRD. Moreover, metabolic syndrome is beginning to emerge in people with CF, especially when treated with ETI [143, 144], and may elevate their cardiovascular risk [145], particularly in those who did not receive CFTR modulator therapy during childhood and potentially experienced years of chronic inflammation.

The goal of the MCFC is to use prospective data to study the impacts of these novel treatments on glycaemia using both OGTT and CGM, as well as on all cardiometabolic factors. This effort aims to improve current patient care and inform future treatments over the long term.

Points for clinical practice and questions for future research

- Thanks to the current standard of care, cystic fibrosis-related diabetes (CFRD) is no longer preceded by a quicker decrease in pulmonary function or by denutrition.
- Insulin insufficiency is common in people with cystic fibrosis (CF). Added insulin resistance, which may occur as a result of systemic inflammation, can lead to overt CFRD.
- We validate the fact that insulin resistance should be evaluated with dynamic indexes following a glucose charge rather than fasting based indices, because HOMA-IR is not sensitive enough in people with CF.
- Mean glucose decreases slightly in people with CF treated with cystic fibrosis transmembrane conductance regulator modulators, but studies are needed to establish whether the increase of overweight and thus of metabolic syndrome could conversely impact the risk of CFRD in the future.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Provenance: Submitted article, peer reviewed.

All citations followed by an asterisk in the main text (*) are studies issued from the MCFC.

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